e) eluting the DNA from the first column and the RNA from the second column, wherein [the two buffers comprise] a first buffer is utilized to lyse cells containing the DNA and RNA and [a second buffer] also to attach the DNA to the first column and [the] a second buffer is used to attach RNA to the second column.

REMARKS

Claims 1-25 are rejected under 25 U.S.C. § 103(a) as being unpatentable over Ekenberg (USPN. 6,218,531) in view of Chakrabarti et al. (Int. J. Radiat. Biol., Vol. 75(8), pp. 1055-1065, 1999). Applicant requests clarification as to the status of remaining claims 26-27.

Independent claims 1, 2, 5, 9, 10, 13 and 26 have been amended to recite that the step of labeling genetic material occurs at the same time fragmentation occurs. Support for this recitation is found on page 14, lines 16-18, and FIG. 2 A.

Claim 10, 13, and 26 have been amended to more clearly recite the invention. Support for the two-buffer isolation process is found throughout the specification, and particularly on page 5, lines 1-7, page 7, lines 19-20 and in FIG 1A-1B.

Ekenberg/Chakrabarti Combination Impermissible Hindsight

Claims 1-25 are rejected under 25 U.S.C. § 103(a) as being unpatentable over Ekenberg (USPN. 6,218,531) in view of Chakrabarti et al. (Int. J. Radiat. Biol., Vol. 75(8), pp. 1055-1065, 1999).

Applicants submit that the proposed combination is impermissible. This is because Ekenberg destroys DNA (via its reliance on DNase), while Chakrabarti seeks to label it. The removal of DNA is crucial to enhance Ekenberg's hybridization signal related to RNA. (See last two lines of Ekenberg's Abstract, and also Column 6, lines 45-53. Column 7, lines 30-32, Column 8, line 4-6.) By contrast, Chakrabarti works *only* with DNA.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive to

supporting the combination. *See ACS Hospital Systems, Inc. v. Monteflore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). One skilled in the art would have a disincentive to combine Ekenberg and Chakrabarti due to a possible destruction of DNA resulting from such a combination.

If the impermissible combination of Ekenberg and Chakrabarti occurs, then no labeling of ***any*** nucleic acids would occur. This is because Ekenberg destroys DNA and Chakrabarti works only with DNA. Also, Chakrabarti does not teach labeling of RNA. Lastly, neither Chakrabarti nor Ekenberg disclose a method for using radical chemistry to label nucleic acids, generally.

In light of the foregoing, Applicants submit that the obviousness rejection based on Ekenberg and Chakrabarti is impermissible. Withdrawal of the §103 rejection is respectfully solicited.

Chakrabarti teaches away
from invented single fractionation-
labeling reaction mechanism

Chakrabarti does not label genetic material, but rather seeks to quantify the number of aldehyde groups on DNA's furanose moiety to determine the extent of DNA damage. If labeling of those aldehyde groups occurs during DNA fragmentation (as is the case in the instant process), intermediate aldehyde groups would be counted, leading to false positives. Rather, Chakrabarti requires that labeling occurs well after (two hours after) fragmentation. (See page 1060, Column 2, lines 14-20.) Specifically, Chakrabarti states as follows:

> "...the present method will be more useful if the DNA is labeled *after* rather than *during* the reaction, in all subsequent bleomycin experiments the fluorescent probe(s) were added to bleomycin-treated samples approximately 2 h following addition of the DNA-damaging agents. ..." (*italicized* emphasis in the original).

The now claimed invention teaches a labeling of DNA at the same time that fragmentation occurs. In other words, radical treatment and labeling occurs at the same time in the instant method. That is why the *entire process* takes less than 20

minutes.

Chakrabarti teaches away from fragmenting and labeling nucleic acid at the same time and as part of the same reaction, as taught by the instant invention. If the simultaneous protocol of the instant invention is attempted in Chakrabarti, intermediate aldehydes form, resulting in detection of a false number of aldehyde-containing sites in Chakrabarti. Chakrabarti's objective would not be fulfilled.

If a prior art reference is cited that requires some modification in order to meet the claimed invention and such modification destroys the purpose of the invention disclosed in the reference, one of ordinary skill in the art would not find reason to make the proposed modification. In re Gordon 733 F. 2d 900 (Fed. Cir 1984). Per In re Gordon, Chakrabarti is inapplicable as a prior art reference.

In contrast, the instant process of isolating, fragmenting, and labeling genetic materials occurs as part of a single reaction.

Ekenberg does not suggest the use of radical-driven chemistry to label genetic material. The inherent nature of the radical-mediated reactions utilized in the present invention (as originally recited in claims 5, 9, 10, and 13 and as now recited in claims 1 and 2) is vastly different from the chemistry employed in Ekenberg. Instead of radical chemistry, Ekenberg employs adsorption of RNA to silica supports (an ionic interaction) merely to isolate the RNA from detritus. As noted supra, that detritus includes DNA.

Also, neither Ekenberg nor Chakrabarti suggest the use of a two buffer process, as recited in claims 9, 10 and 13, and newly added claim 26. Rather, and as stated by the Examiner on page 3, of the Office Communication and in Ekenberg, col. 7, lines 26-42, Ekenberg requires several buffers, thereby adding to the complexity and total time to complete the processes.

Lastly, neither Ekenberg nor Chakrabarti anticipate or suggest the use of anaerobic radical-based chemistry environs to label DNA and RNA, as recited in claim 8. This is because no purposeful steps are undertaken in the references to remove oxygen. To otherwise assert that the references suggest anaerobic conditions without

even a mention in the references of aerobic or anaerobic conditions is impermissible hindsight.

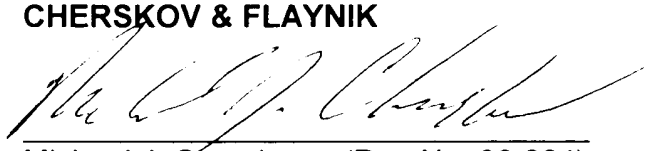
The use of anaerobic conditions in the present invention led to unexpected results. The inventors found that, at least for Op-Cu oxidation protocols, a 15 percent increase in hybridization signal was realized when anaerobic conditions were utilized (see original specification, page 14, lines 10-12). Because anaerobic conditions lead to a substantial increase in the hybridization signal in the instant invention, and because none of the art of record even suggests aerobic or anaerobic environs, Applicant submits that the recitation of anaerobic conditions is patentable over said art.

In light of the foregoing, Applicants submit that the §103 rejections based on Ekenberg and Chakrabarti are obviated. Withdrawal of the rejection and allowance of claims 1-27 is respectfully requested.

An earnest attempt has been made hereby to respond to the §103 rejection contained in the November 19, 2002 Office Communication. It is submitted that all remaining claims are of proper form and scope for allowance. If the Examiner feels that a telephonic interview would expedite allowance of this application, she is respectfully urged to contact the undersigned. Allowance of claims 1-27 is respectfully solicited.

Respectfully submitted,

CHERSKOV & FLAYNIK



Michael J. Cherskov (Reg No. 33,664)

1. (Thrice Amended) A method for labeling genetic material, the method comprising:

a) disrupting cells so as to liberate genetic material contained in the cells;

b) contacting the genetic material to a column in a manner to cause the genetic material to become immobilized to the column;

c) fragmenting and labeling the immobilized genetic material within the column at the same time via a radical-mediated process; and

d) eluting the labeled material from the column, wherein the method occurs within 20 minutes.

2. (Thrice Amended) A method for labeling genetic material, the method comprising:

a) disrupting cells so as to liberate genetic material contained in the cells;

b) contacting the genetic material to a column in a manner to cause the genetic material to become immobilized to the column;

c) fragmenting and labeling the immobilized genetic material at the same time via a radical-mediated procedure; and

d) eluting the labeled material from the column wherein the step of labeling the genetic material further comprises maintaining the column at a temperature of between 45 °C and 100 °C.

5. (Thrice Amended) A method for labeling genetic material, the method comprising:

a) disrupting cells so as to liberate genetic material contained in the

cells;

b) contacting the genetic material to a column in a manner to cause the genetic material to become immobilized to the column;

c) fragmenting and labeling the immobilized genetic material at the same time; and

d) eluting the labeled material from the column wherein the step of labeling the genetic material comprises:

e) contacting double-stranded nucleic acid molecules of the genetic material with radical-generating complexes for a time and at concentrations sufficient to produce free-aldehyde moieties;

f) reacting the aldehyde moieties with amine to produce a condensation product; and

g) contacting the condensation product with a chromophore.

9. (Thrice Amended) A two-buffer process for [manipulating] labeling genetic material, the process comprising:

a) contacting cells containing the genetic material to a silica column;

b) creating a first fraction of cell detritus and a second fraction containing the genetic material;

c) confining the genetic material to the column;

d) removing the cell detritus;

e) subjecting the genetic material to radicals so as to produce reactive aldehyde groups on the genetic material; and

f) attaching chromophore to the genetic material wherein the genetic material is contacted with radical in aerobic conditions wherein the steps of attaching chromophore occurs at the same time that the reactive aldehyde groups are produced.

10. (Thrice Amended) A two-buffer process for isolation of genetic material, followed by labeling of the genetic material, the process comprising:

a) contacting cells containing the genetic material to a silica column;

b) creating a first fraction of cell detritus and a second fraction containing the genetic material;

c) confining the genetic material to the column;

d) removing the cell detritus;

e) subjecting the genetic material to radicals so as to produce reactive aldehyde groups on the genetic material; and

f) attaching chromophore to the genetic material wherein the genetic mate rial is contacted with radical in anaerobic conditions , wherein the steps of attaching chromophore occurs at the same time that the reactive aldehyde groups are produced.

13. (Thrice Amended) A two-buffer process for isolation of genetic material, followed by labeling of the genetic material, the process comprising:

a) contacting cells containing the genetic material to a silica column;

b) creating a first fraction of cell detritus and a second fraction containing the genetic material;

c) confining the genetic material to the column;

d) removing the cell detritus;

e) subjecting the genetic material to radicals so as to produce reactive aldehyde groups on the genetic material; and

f) attaching chromophore to the genetic material wherein the two buffers comprise a first buffer to lyse the cells and a second buffer to attach the genetic material to the column , wherein the steps of attaching chromophore occurs at the same time that the reactive aldehyde groups are produced.

26. (Amended) A [two buffer] process for [fractionating] fragmenting and labeling DNA and RNA contained in a lysate, the process comprising:

a) contacting the lysate with a first column packed with material so as to confine the DNA to the first column and allow the RNA to pass through the first column;

b) contacting the passed through RNA to a second column packed with material so as to confine the RNA to the second column;

c) subjecting the confined DNA and confined RNA to radicals so as to produce reactive aldehyde groups on the DNA and RNA;

d) attaching chromophore to the DNA and RNA wherein the steps of attaching chromophore occurs at the same time that the reactive aldehyde groups are produced; and

e) eluting the DNA from the first column and the RNA from the second column, wherein [the two buffers comprise] a first buffer is utilized to lyse cells containing the DNA and RNA and [a second buffer] also to attach the DNA to the first column and [the] a second buffer is used to attach RNA to the second column.